

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-60 are in this case. Claims 8-14, 21-44 and 53-60 were withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to a non-elected species. Claims 1-7, 15-20 and 45-52 have been rejected. Claims 17-18 and 20 have now been canceled. Claims 1, 3-5, 7, 15, and 45-52 have now been amended. New Claims 61 and 62 have now been added.

Priority

The Examiner has indicated the specific procedures to be followed to enable Applicant to claim priority under 35 U.S.C. 120, 121 and 365(c).

Applicant therefore currently elects to insert as the first paragraph of the specification, the following text:

This application claims the benefit of priority of PCT/IL00/00514, filed August 29, 2000, which claims the benefit of priority of U.S. Patent Application No. 09/385,411, filed August 30, 1999, now abandoned, the contents of which are hereby incorporated by reference.

In view of the above amendment, Applicant believes to have fulfilled the necessary requirements for enabling claiming of priority by the instant application of PCT/IL00/00514, filed August 29, 2000 and U.S. Patent Application No. 09/385,411.

Specification

The Examiner has objected to the abstract of the disclosure as a consequence of same being included only on the cover page of a WO publication instead of on a separate page.

Applicant therefore currently elects to amend the specification by inserting new page 65, following the last page of the claims section, reciting the following text:

ABSTRACT OF THE DISCLOSURE

A method of preventing, inhibiting and/or reversing proliferation, colonization, differentiation and/or development of abnormally proliferating cells in a subject is disclosed. The method is effected by administering to the subject a therapeutically effective amount of a

ribonuclease of the T2 family.

In view of the above amendment, Applicant believes to have overcome the objection relating to the abstract of the disclosure.

Information Disclosure Statement

The Examiner states that the information disclosure statement filed 12-27-02 fails to comply with 37 CFR 1.98(a)(2) as a consequence of there being no copy of cited references: Kawata et al. 1988. Eur J Biochem. 176:683-697; Irie *et al.*, 1999. Pharmacol Ther. 81:77-89; and Roiz *et al.*, 2000. J Amer Soc Hort Sci. 125:9-14.

Applicant wishes to inform the Examiner that Applicant's records show that the cited references were indeed included with the IDS of 12-27-02. Nevertheless, in order to facilitate prosecution of the instant application and as a courtesy to the Examiner, Applicant currently encloses a copy of the cited references.

In view of such document enclosure, Applicant believes to now being in compliance with 37 CFR 1.98(a)(2) with respect to these references.

35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner has rejected claims 1-7, 46-48 and 52 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner's rejections are respectfully traversed. Claims 1, 46-48 and 52 have now been amended.

The Examiner contends that the term "and/or" in claims 1, 46-48 and 52 is vague and renders the claims indefinite, and that changing the term "and/or" to "or... or both" would be remedial. The Examiner further contends that claims 2-7 which depend from claim 1 fail to clarify the indefiniteness.

Applicant respectfully traverses the Examiner's contention that the term "and/or" in claims 1, 46-48 and 52 is vague and renders the claims indefinite. With respect to claim 1, Applicant wishes to respectfully point out that there are in fact two instances of the term "and/or" and that the Examiner has not specified which of the two is vague and renders the claim indefinite. Regardless, in all instances cited by the Examiner, the term "and/or" is used to specify any combination of three elements, namely, "preventing", "inhibiting" and "reversing" in claims 1, 46-48 and 52; and

“colonization, “differentiation” and “development” in claim 1. However, the Examiner’s suggestion to change the term “and/or” to the format “or... or both,” by virtue of reciting “both” only addresses two elements of the three. Applicant is therefore of the opinion that the use of the format “or... or both,” as suggested by the Examiner, would in fact render the claims less definite than the use of the term “and/or”.

Nevertheless, in the interest of expediting prosecution of the instant application, Applicant has elected to amend claims 1, 46-48 and 52 so as to replace the recitation “*preventing, inhibiting and/or reversing*” with the recitation “*preventing, inhibiting or reversing*”, to thereby overcome the Examiner’s rejection.

Applicant further currently elects, in the interest of expediting prosecution of the instant application, to amend claim 1 so as to replace the recitation “*colonization, differentiation and/or development*” with the Markush group-based recitation “*process... selected from the group consisting of proliferation, development, differentiation, transformation, tumorigenesis, tumor growth, colonization and angiogenesis*”, to thereby overcome the Examiner’s rejection.

The Examiner has rejected claims 1-7 and 45-52 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps (MPEP § 2172.01), the omitted steps being whether the objective of the methods has been achieved, such as whether the tumor has been ameliorated, whether the tumor growth has been inhibited, and whether the number and size of the tumor have been reduced. The Examiner’s rejections are respectfully traversed. Claims 1 and 45-52 have now been amended.

Applicant currently elects to amend claim 1 to include the terminal recitation “*thereby preventing, inhibiting or reversing in a mammalian subject, said process associated with abnormally proliferating cells*”.

Applicant currently elects to amend claim 45, to include the terminal recitation “*thereby treating the tumor in a mammalian subject.*”

Applicant currently elects to amend claim 46, to include the terminal recitation “*thereby preventing, inhibiting or reversing the development of a tumor in a mammalian subject.*”,

Applicant currently elects to amend claim 47, to include the terminal recitation “*thereby preventing, inhibiting or reversing transformation of a benign tumor to a*

malignant tumor in a mammalian subject.”

Applicant currently elects to amend claim 48, to include the terminal recitation *“thereby preventing, inhibiting or reversing tumor angiogenesis in a mammalian subject.”*

Applicant currently elects to amend claim 49, to include the terminal recitation *“thereby reducing the number of individual tumors in a mammalian subject.”*

Applicant currently elects to amend claim 50, to include the terminal recitation *“thereby reducing tumor size in a mammalian subject.”*

Applicant currently elects to amend claim 51, to include the terminal recitation *“thereby reducing a number of malignant tumors in a mammalian subject.”*

Applicant currently elects to amend claim 52, to include the terminal recitation *“thereby preventing, inhibiting or reversing transformation of a tissue into a tumor in a mammalian subject.”*

The Examiner contends that there is insufficient antecedent basis for the recitation *“wherein the abnormally proliferating cells are cancerous cells”* of claim 17, and for the recitation *“wherein the abnormally proliferating cells are cells”* of claim 18.

In order to overcome the Examiner’s rejections, Applicant currently elects to now cancel claims 17-18, thereby rendering moot the Examiner’s rejections of these claims.

In view of the arguments and amendments set forth above, Applicant believes to have overcome the 35 U.S.C. § 112, second paragraph, rejections.

35 U.S.C. § 112, First Paragraph, Rejections

The Examiner has rejected claims 1-7, 15-20 and 45-52 under 35 U.S.C. § 112, first paragraph as not enabling a person skilled in the relevant art to use the invention commensurate in scope with these claims. The Examiner's rejections are respectfully traversed. Claims 1, 3-5, 7, 15 and 45-52 have now been amended. Claims 17-18 and 20 have now been cancelled rendering moot the Examiner’s rejections of these claims. New Claims 61 and 62 have now been added.

The Examiner concedes that the specification is enabling for: (i) preventively reducing the number of aberrant crypt foci (ACF) in a rat when RNase B1 is administered directly to the colon via osmotic micro-pump; (ii) reducing the number

of colon tumors, the tumor size, the number of ACFs or tumor angiogenesis in a rat with oral administration of RNase B1 microcapsules; and (iii) reducing the number and size of tumors, inhibiting the growth of tumors and reducing angiogenesis of tumor in rats treated with osmotic pumps that directly deliver RNase B1 to the colon. The Examiner nevertheless concludes that the instant specification does not enable one of ordinary skill in the art to use the invention commensurate in scope as claimed.

In particular, the Examiner contends that the specification does not reasonably provide enablement for claimed methods of the instant invention by using any ribonuclease of the T2 family or its mutants that substantially lack ribonuclease activity.

The Examiner further particularly contends that the specification fails to provide adequate guidance and evidence as to how to administer sufficient RNase of T2 family to target cells, such as brain tumor cells, renal cancer cells, or prostate cancer cells, via oral administration, cutaneous or subcutaneous administration, or intramuscular administration. The Examiner quotes as grounds for such contention passages of the specification relating to the higher anti-tumor effect of RNase B1 obtained when administered via colon-implanted osmotic micro-pumps as opposed to that obtained when the RNase is administered orally via microcapsules. The Examiner concludes on the basis of such differences in therapeutic effect that the administration route plays a critically relevant role in the efficiency of delivering the protein to target cells and providing therapeutic effects *in-vivo*, and contends that the specification fails to provide sufficient enabling disclosure for the full scope of the invention claimed.

The Examiner yet further particularly contends that in light of the absence of knowledge regarding the structural basis for the obtained therapeutic effect of RNase B1, one skilled in the art at the time of the invention would not know how to use the claimed T2 family ribonuclease or mutants thereof substantially lacking ribonucleolytic activity or a pharmaceutical composition comprising said ribonuclease to practice the full scope of the claimed invention.

Applicant strongly disagrees with the Examiner's contention that the specification does not reasonably provide enablement for claimed methods of the instant invention by using any ribonuclease of the T2 family or its mutants that substantially lack ribonuclease activity. Applicant further strongly disagrees with the

Examiner's contention, based on a putative absence of knowledge regarding the structural basis for the obtained therapeutic effect of RNase B1, that one skilled in the art at the time of the invention would not know how to use the claimed T2 family ribonuclease or mutants thereof substantially lacking ribonucleolytic activity or a pharmaceutical composition comprising said ribonuclease so as to practice the invention over the full scope claimed.

Applicant is of the very firm opinion that the great structural similarities shared by T2 family ribonucleases, which indeed serve to group all such ribonucleases as a single family, are such that the ordinarily skilled artisan will understand that all such ribonucleases indeed possess the same or similar functional capacities as RNase B1 with respect to regulation of mammalian cellular processes such as proliferation, development, differentiation, transformation, tumorigenesis, tumor growth, colonization and angiogenesis. The highly significant similarities serving to group ribonucleases as members of the T2 family, which inherently endow such ribonucleases with the same or similar functional capacities as RNase B1 with respect to regulation of claimed processes associated with proliferating mammalian cells, are clearly set forth in the specification at page 5, "T2-RNases; page 14, last paragraph; and page 15, Table 1. Indeed at the time the invention was made the great structural and functional similarities between the different T2 family RNases had been extensively characterized and demonstrated. For example, T2 family ribonucleases were known to share critical structural/functional features such as five conserved disulfide bridges and two conserved active site segments (CAS), and a composition of about 200 amino acid residues (refer, for example, to enclosed article of Irie, 1999, throughout the article, and in particular at page 78, "2.1 Acid Ribonucleases from Fungi", and the extensively detailed conserved homology diagram at page 79).

As such, Applicant is of the very strong opinion that the specification does indeed reasonably provide enablement for claimed methods of the instant invention by using any ribonuclease of the T2 family or its mutants that substantially lack ribonuclease activity. Furthermore, Applicant is of the very strong opinion that, in light of the above-described great structural/functional similarities shared by T2 family RNases, one skilled in the art at the time of the invention would be able to use, in conjunction with routine experimentation as appropriate, any ribonuclease of the T2 family or mutants thereof substantially lacking ribonucleolytic activity or a

pharmaceutical composition comprising such ribonuclease so as to practice the invention over the full scope claimed.

Applicant further strongly disagrees with the Examiner's contention that the specification fails to provide adequate guidance and evidence as to how to administer sufficient RNase of T2 family to various non-colon types of abnormally proliferating cells, via various modes of administration.

Applicant wishes to firstly and respectfully point out that the Examiner appears to have inappropriately linked claim 5, drawn to different administration modes, with claim 4, drawn to different types of diseases, so as to conclude that what must necessarily be enabled by the instant specification is the use of each of the claimed administration modes for treating each of the claimed diseases. In Applicant's very firm opinion, this is clearly incorrect since claims 4 and 5 each depend from claim 1 such that one does not depend from the other, as apparently misinterpreted by the Examiner. As such, Applicant is of the very strong opinion that the Examiner's rejections relating to the route of administration are invalid by virtue of being founded on a clear misinterpretation of the dependency relationships between claims 1, 4 and 5.

Moreover, Applicant wishes to respectfully express the very strong opinion that the basis upon which the Examiner makes the contention that administration mode is of relevant importance is inherently flawed. Namely, the Examiner bases this contention on the lower therapeutic effectiveness obtained when administering RNase orally via microcapsules as opposed to that obtained when administering the RNase via intra-colonic osmotic pump. Applicant wishes to respectfully point out that the instant invention is drawn to the use of T2 family RNase as therapeutic agent effective against abnormally proliferating cells, such as tumor cells, in a mammalian subject. As is clearly shown in the Examples of the instant application the effect of T2 RNases on abnormally proliferating cells is not administration mode-dependent but rather concentration-dependent. Thus, the mode of administration *per se* is purely incidental to the invention since the amount of RNase used in each administration mode can easily be adjusted so as to achieve an effective cellular concentration without requiring one of ordinary skill in the art to engage in undue trial and error experimentation.

For example, oral administration of T2 family RNase via microcapsules could

easily be optimized for satisfactory therapeutic effectiveness by one of ordinary skill in the art. Microencapsulation sheaths of digestive tract degradabilities suitable for achieving desired release of T2 family RNase at a particular location in the digestive tract, such as in the colon, could be easily identified through routine experimentation. In any case, in Applicant's firm opinion, such experimentation was not necessary at the time the instant invention was made since at such time microcapsule delivery of drugs, such as polypeptide drugs, via the oral route to digestive tract locations, such as the colon, had been highly optimized and was routinely practiced in the art (refer, for example, to enclosed abstracts of: Hu *et al.*, 1999; Ishibashi *et al.*, 1999; Matsuda *et al.*, 1996; Takaya *et al.*, 1995; Tozaki *et al.*, 1997 and Tozaki *et al.*, 1999). As such, since the foundation upon which the Examiner's rejections relating to the route of administration is clearly invalid, Applicant firmly believes such rejections to be clearly unjustified.

Above and beyond the aforementioned arguments traversing the Examiner's rejections relating to the route of administration, Applicant wishes to further point out that while the high therapeutic effectiveness obtained when administering the RNase via intra-digestive tract osmotic pump provides support for such administration being a suitable mode of administration for treatment of a digestive tract disease, such as colon cancer, such demonstration must be seen as a working example which can be broadly adapted by the ordinarily skilled artisan towards treatment of various types of diseases associated with abnormally proliferating cells, as expressly stated by the specification (page 35, paragraph starting at line 25; and page 55, final paragraph). Applicant is of the very strong opinion that, in sharp contrast with the Examiner's contention, it was in fact well within the purview of one of ordinary skill in the art at the time the instant invention was made to achieve, according to the teachings of the instant specification, and in conjunction with routine experimentation as appropriate, satisfactory delivery of T2 family RNase to essentially any desired target tissue via a suitable route, so as to enable practicing of the instant invention according to the full scope claimed. With respect thereto, Applicant wishes to respectfully point out that at the time the instant invention was made the state-of-the-art relating to *in-vivo* delivery of polypeptides to specific body tissues was considered sufficiently highly advanced as to enable satisfactory and controlled delivery of polypeptides to essentially any body tissue. This was clearly highlighted at such time by the routine issuing of U.S.

Patents including claims drawn to delivery of polypeptides via any of various routes (refer, for example, to U.S. Patent 6,416,960, claim 36, drawn to delivery of the polypeptide luciferase via the topical, enteric, local, parenteral, intracystic, intracutaneous, intravitreal, subcutaneous, intramuscular, or intravenous route; U.S. Patent No.: 6,075,009, claim 31, drawn to delivery of a polypeptide via the buccal, sublingual, dermal, intraocular, subcutaneous, intradermal, intramuscular, intravenous, intraarticular, or transdermal route; and U.S. Patent No.: 6,306,832, claim 28, drawn to delivery of a polypeptide via the intravenous, parenteral, oral, topical, or inhalation route). On the basis of these arguments alone, Applicant is of the very strong opinion that the instant specification is indeed sufficiently enabling so as to enable one of ordinary skill in the art to practice the instant invention over the full scope claimed. Applicant wishes to wishes to vigorously emphasize that the instant specification indeed provides sufficient and ample guidance enabling practicing of the instantly taught method with respect to non-colon types of abnormally proliferating cells. In particular, extensive guidance in this respect is provided in the specification starting from page 24, line 27 to page 30, line 31.

Critically, subsequent to filing of the specification, Applicant has generated experimental results (refer to the enclosed Declaration by Prof. Oded Shoseyov, and the enclosed Appendix associated therewith) conclusively proving that the specification indeed enables the ordinarily skilled artisan to use the invention commensurate in scope with the claims, namely whereby (i) the RNase is any of various RNases of the T2 family; (ii) the administration of the RNase is effected via any of various routes; (iii) the abnormally proliferating cells are cancer cells of any of various types; and (iv) the process associated with abnormally proliferating cells is any of various relevant pathogenic processes. In particular, the experimental results discussed in the Declaration and in the Appendix conclusively demonstrate that the instant specification indeed enables the ordinarily skilled artisan to practice the invention commensurate in scope with the claims, in particular whereby:

(i) The T2-family RNase belongs to various members of the T2 RNase family derived from highly phylogenetically divergent sources, including the prokaryote-derived RNase I, the fungal (*A. oryzae*)-derived RNase T2 (Appendix, page 1, Figure 1), the mammalian/human-derived RNase 6PL (Appendix, page 2, Figures 2-5), or RNase B1 (Appendix, pages 3-10, Figures 6-15);

(ii) The administration route is one of various administration routes, including the systemic/intravenous (Appendix: page 3, Figure 7; page 8, Figure 9), systemic/intraperitoneal (Appendix: page 3, Figure 6; page 4, Figures 8-9; page 8, Figures 12-14), and the local/subcutaneous route (Appendix, page 6, Figures 10-11);

(iii) The abnormally proliferating cells are various types of cancer cells, including melanoma cells (Appendix, page 3, Figures 6-11), mammary carcinoma cells (Appendix, page 7, Table 1) or colon carcinoma cells (Appendix: pages 8-10, Figures 9-15 and Table 1); and

(iv) The process associated with abnormally proliferating cells is one of various such processes, including proliferation/growth (Appendix: pages 3-5, Figures 6-9; page 8, Figure 12), colonization/metastasis (Appendix: pages 3-5, Figure 7; page 7, Table 1; page 10, Table 1), and/or angiogenesis/a pro-angiogenic process (Appendix: page 5, Figure 6; page 6, Figures 10-11; page 9, Figure 15).

In view of these highly conclusive experimental results, Applicant is of the very strong opinion that the Examiner's rejections are unfounded.

Nevertheless, in the interest of expediting prosecution of the instant application, Applicant currently elects to: (i) amend claim 1, as described above, so as to replace the limitation of preventing, inhibiting and/or reversing proliferation, colonization, differentiation and/or development of abnormally proliferating cells with that of preventing, inhibiting or reversing in a mammalian subject, a process associated with abnormally proliferating cells selected from the group consisting of proliferation, development, differentiation, transformation, tumorigenesis, tumor growth, colonization and angiogenesis; (ii) amend claim 3, which depends from Claim 1, to now include the limitation of the abnormally proliferating cells being angiogenic cells; (iii) amend Claim 5, depending from Claim 1, to now include the limitation of the administration route being intravenous, subcutaneous and/or systemic; (iv) amend Claim 7, depending from Claim 1, to now include the limitation of the RNase being RNase I or RNase 6PL; (v) amend Claims 45-52 to now include the limitation of a mammalian subject; (vi) add New Claim 61, depending from Claim 1, including the limitation of the differentiation being malignant differentiation; (vii) add New Claim 62, depending from Claim 1, including the limitation of the angiogenesis being tumor angiogenesis; (viii) amend Claim 15 to now include the limitation of the RNase being substantially purified, and being derived from

Aspergillus niger and/or being substantially deglycosylated. It will be appreciated by the ordinarily skilled artisan that the deglycosylated RNase having the claimed activities has various clear utilities and advantages, including: (a) affording the possibility to be produced in a prokaryote which does not glycosylate, or which abnormally glycosylates, the RNase; (b) potentially being simpler and more economically advantageous to produce than a glycosylated form thereof; and (c) avoidance of immune-rejection when administered to a subject capable of mounting an immune reaction against a glycosylated epitope of the non deglycosylated RNase. As described in the specification, the deglycosylated RNase B1 unexpectedly retained the capacity to regulate the claimed processes in abnormally proliferating mammalian cells.

Support for the claim 1 amendment limiting the process associated with abnormally proliferating cells to transformation is provided in the specification at page 16, sentence starting at line 12. Support for the claim 1 and claim 61 amendments limiting the process to differentiation, and malignant differentiation, respectively, is provided in the specification at page 50, “The effect of RNase B1 as a preventive agent”. Support for the claim 1 amendment limiting the process to tumorigenesis is provided in the specification at page 47, “EXAMPLE 4 The in vivo effect of RNase B1 on tumor development in a rat model”. Support for the claim 1 amendment limiting the process to tumor growth is provided in the specification at page 21, sentence starting at line 20. Support for the claim 1 amendment and new claim 62 limiting the process to angiogenesis or tumor angiogenesis, respectively, is provided in the specification at page 50, paragraph starting at line 33. Support for the the claim 1 and claim 45-52 amendments limiting the subject to a mammalian subject is provided in the specification at page 47, EXAMPLE 4. “The in vivo effect of RNase B1 on tumour development in a rat model”. Specification support for the limitation of the RNase being derived from Aspergillus niger is provided in the Examples section, for example at page 37 “Preparation and purification of A. niger extracellular RNase”. Specification support for the limitation of the ribonuclease being substantially deglycosylated is provided, for example, at page 37, paragraph starting at line 32. Specification support for the limitation of the RNase being RNase T2, RNase I or RNase 6PL is provided at pages 19-20, Table 2. Specification support for the limitation of the abnormally proliferating cells being angiogenic is provided,

for example, at page 51, sentence starting at line 1; and at page 23, paragraph starting at line 17, in particular line 25. Specification support for the limitation of the administration route being intravenous and/or subcutaneous is provided, for example, at page 25, paragraph starting at line 18. Specification support for the limitation of the administration route being systemic is provided, for example, at page 25, sentence starting at line 27.

In view of the arguments and amendments set forth above, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph, rejections.

35 U.S.C. § 102(b) Rejections - Ohgi et al., 1991

The Examiner has rejected claims 15, 17, 18 and 20 under 35 U.S.C. § 102(b) as being anticipated by Ohgi et al. The Examiner's rejections are respectfully traversed. Claim 15 has now been amended. Claims 17-18 and 20 have now been canceled, rendering moot the Examiner's rejection of these claims.

The Examiner contends that claims 15, 17, 18 and 20 are directed to a pharmaceutical composition comprising a ribonuclease of the T2 family, such RNase Rh, and a pharmaceutically acceptable carrier. The Examiner further contends that Ohgi teaches purified RNase Rh dissolved in a buffer constituting a pharmaceutically acceptable carrier, and that as such claims 15, 17, 18 and 20 are anticipated by Ohgi.

In the interest of expediting prosecution of the instant application, Applicant currently elects to amend claim 15, as described above, to now include the limitation of the RNase being derived from Aspergillus niger and/or being substantially deglycosylated.

Since Ohgi neither teaches, exemplifies nor suggests any RNase which is derived from *Aspergillus niger*, a mammal or a bacterium, and/or which is substantially deglycosylated, Applicant believes that the claims amendments described above overcome the 35 U.S.C. § 102(b) rejections relating to Ohgi.

35 U.S.C. § 102(b) Rejections - Roiz et al., 1995

The Examiner has rejected claims 1-2, 6 and 15-20 under 35 U.S.C. § 102(b) as being anticipated by Roiz et al., 1995. The Examiner's rejections are respectfully traversed. Claims 1 and 15 have now been amended. Claims 17-18 and 20 have now been canceled, rendering moot the Examiner's rejection of these claims.

The Examiner contends that claims 1-2, 6 and 15-20 are directed to a method of inhibiting proliferation, differentiation, or development of abnormally proliferating cells in a subject by using any ribonuclease of the T2 family, such as RNase B1, and a pharmaceutically acceptable carrier. The Examiner further states that Roiz teaches preparing stigmatic RNase B1 by soaking stigmas in a 20 mM Tris-HCl buffer to allow proteins to diffuse into the buffer, separating the proteins via SDS-PAGE, dissecting the protein band from the gel and using it to inhibit pollen germination and pollen tube length. The Examiner concludes that, as such, Roiz shows that stigmatic RNase B1 inhibits proliferation or development of abnormally proliferating cells in a subject (pollen). The Examiner further states that the SDS-PAGE gel will denature the RNase B1 protein and substantially inactivate its ribonucleolytic activity, and that the buffer solution containing the RNase B1 is considered a pharmaceutically acceptable carrier. The Examiner concludes that, as such, claims 1-2, 6 and 15-20 are anticipated by Roiz. The Examiner further states that the term “pharmaceutical” does not carry weight when considering a 102 rejection.

Applicant strongly disagrees with the Examiner’s contention that Roiz *et al.* teaches inhibition of proliferation of abnormally proliferating cells in a subject on the grounds that the proliferating pollen cells whose proliferation or development is inhibited according to the teachings of Roiz *et al.* are in fact normally proliferating pollen cells, and not abnormally proliferating cells as incorrectly characterized by the Examiner. Furthermore, Roiz *et al.* teaches only partially purified RNase (Roiz *et al.*, page 38, column 1, “Partial Purification and Analysis of Stigmatic RNase”), whereas in critically sharp contrast, the instant invention teaches purified RNase (specification, page 37, “Preparation and purification of *A. niger* extracellular RNase”). Moreover, Roiz *et al.* critically teaches a plant subject whereas the instant invention, in sharp and significant contrast, teaches a mammalian subject.

Nevertheless, in the interest of expediting prosecution of the instant application, Applicant currently elects to amend claim 1, as described above, to now include the limitation of the subject being a mammalian subject, and to amend claim 15, to now include the limitation of the ribonuclease being substantially purified.

Since neither a subject having abnormally proliferating cells, nor a mammalian subject, nor substantially purified RNase is taught, exemplified, or suggested by Roiz *et al.*, Applicant believes that the arguments and claim amendments described above

overcome the 35 U.S.C. § 102(b) rejections relating to Roiz *et al.*

35 U.S.C. § 102(b) Rejections - Kawata et al., 1990

The Examiner has rejected claims 15-18 and 20 under 35 U.S.C. § 102(b) as being anticipated by Kawata et al., 1990. The Examiner's rejections are respectfully traversed. Claim 15 has now been amended. Claims 17-18 and 20 have now been cancelled, rendering moot the Examiner's rejection of these claims.

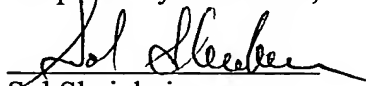
The Examiner contends that claims 15-18 and 20 are directed to a pharmaceutical composition comprising a ribonuclease of the T2 family, such as RNase T2, or a ribonuclease substantially lacking ribonuclease activity, and a pharmaceutically acceptable carrier. The Examiner states that Kawata teaches dissolving RNase T2 protein in 0.1 M citrate buffer at various pH and adding diethyl pyrocarbonate in 10 % dioxane to the solution so as to inactivate RNase ribonucleolytic activity. The Examiner further states that the buffer solution containing the RNase T2 protein or inactivated RNase T2 protein is considered a pharmaceutically acceptable carrier.

In the interest of expediting prosecution of the instant application, Applicant currently elects to amend claim 15, as described above, to now include the limitation of the RNase being derived from *Aspergillus niger* and/or being substantially deglycosylated.

Since no RNase being derived from *Aspergillus niger* and/or being substantially deglycosylated is taught, exemplified, or suggested by Kawata *et al.*, Applicant believes that the claim amendments described above overcome the 35 U.S.C. § 102(b) rejections relating to Kawata *et al.*

In view of the amendments and remarks set forth above it is respectfully submitted that claims 1-7, 15-16, 19, 45-52, 61 and 62 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,



Sol Sheinbein

Registration No. 25,457

Date: April 19, 2004

Encl.:

A three-month extension fee;

The following Abstracts:

- Abstract of Hu *et al.*, J Drug Target. 1999;6(6):439-48;
- Abstract of Ishibashi *et al.*, J Control Release. 1999 Jun 2;59(3):361-76;
- Abstract of Matsuda *et al.*, J Drug Target. 1996;4(2):59-67;
- Abstract of Takaya *et al.*, J Pharm Pharmacol. 1995 Jun;47(6):474-8;
- Abstract of Tozaki *et al.*, J Pharm Sci. 1997 Sep;86(9):1016-21;
- Abstract of Tozaki *et al.*, Life Sci. 1999;64(13):1155-62;

The following Articles:

- Article of Hu *et al.*, 1991. Proc. Natl. Acad. Sci. U. S. A. 88:2227-31;
- Article of Hu *et al.*, 1993. Proc. Natl. Acad. Sci. U. S. A. 90:1217-21
- Article of Irie *et al.*, 1999. Pharmacol Ther. 81:77-89;
- Article of Kao *et al.*, 2002. Proc. Natl. Acad. Sci. U. S. A. 99:10066-71
- Article of Kawata *et al.* 1988. Eur J Biochem. 176:683-697; and
- Article of Roiz *et al.*, 2000. J Amer Soc Hort Sci. 125:9-14;

A Declaration by Prof. Oded Shoseyov; and

A Curriculum Vitae of Prof. Oded Shoseyov.